REMARKS

The Office Action mailed October 9, 2008 has been carefully considered and the following response prepared.

REJECTION UNDER 35 USC 102(e)

At page 2 of the Office Action, the Examiner maintained the rejection of claims 1-3, 6-8 and 13-15 under 35 USC 102(e) as anticipated by Daniell (U.S. Patent 7,129,391) (the '391 patent") filed May 15, 1998) for the reasons set forth in the Office Action mailed February 19, 2008.

Applicants again traverse this rejection.

In the present Office Action, the Examiner alleged that Applicants have not proven that the claims of the '391 patent are not enabled. To support this position, the Examiner asserted that the '391 patent shows that transformation of soybean plastids using the aadA selection marker is possible, and that Zhang et al. also believed it should be possible to transform soybean plastids. The Examiner found unpersuasive Applicants' arguments in the previously filed response that Dr. Henry Daniell implicitly acknowledged the '391 patent was not a disclosure of fertile transgenic soybeans because of his statements in Daniell et al. (2005) in which he attributes the first successful fertile transplastomic soybean plants to Dufourmantel et al. [referring to Dufourmantel et al. 2003]. The Examiner found Applicants' arguments unpersuasive because Daniell did not say that he attempted soybean transformation and was unsuccessful. Finally, the Examiner dismissed Applicants' arguments on the ground that the claims in the '391 patent are presumed enabled until proven otherwise; and that Dufourmantel et al. demonstrates that '391 patent is enabled.

Applicants again submit that the '391 patent does not enable fertile transplastomic leguminous plants, and therefore does not anticipate claims 1-3, 6-8, and 13-15. Applicants' remarks relating to this rejection in the response filed July 21, 2008 are incorporated herein by reference.

The disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter, such that a person skilled in the art can make and use the subject matter without undue experimentation. Additionally, the specification of a patent, when filed, must enable persons skilled in the art to make and use the invention without undue experimentation. The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to skilled persons and readily available to the public. The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. MPEP 2164.05(a).

The '391 patent issued from application Serial No. 09/079,640 filed May 15, 1998. The '391 patent claims priority of earlier-filed applications, back to 1988; however, as fertile transplastomic leguminous plants were not enabled even at the filing date in 1998, the state of the art at the earlier filing dates does not aid enablement of the claims of the '391 patent with respect to such plants.

The '391 patent discloses universal chloroplast integration and expression vectors which are stated to be competent to stably transform and integrate genes of interest into chloroplast genomes of multiple species of plants. The '391 patent also contains claims to stably transformed plants or progeny thereof which comprise chloroplasts stably transformed with the vectors. In the context of the '391 patent, col. 1, lines 31-36, state that "stably" integrated DNA sequences are those which are inherited through genome replication by daughter cells or organisms, and this stability is exhibited by the ability to establish permanent cell lines, clones or transgenic plants comprised of a population containing the exogenous DNA. At col. 7, lines 10-12, of the '391 patent, "stably" transformed is defined as permanently transformed.

Example 6 of the '391 patent, the only example related to soybean, briefly describes general steps of a plastidial transformation of soybean leaves with a universal chloroplast transformation that contains tobacco chloroplast flanking sequences. Figure 15 shows that some soybean embryonic shoots are resistant to the antibiotic used for selection. There is no disclosure of developed and fertile soybean plants. Similarly, Example 5 of the '391 patent, directed to peanut chloroplast transformation, also only briefly describes general steps of a plastidial transformation with the same universal chloroplast transformation vector. Figure 14 shows that some peanut embryonic shoots are resistant to the antibiotic used for selection. There

is no disclosure of developed and fertile peanut plants. Example 11 discloses progeny of transplastomic tobacco plants that contain a glyphosate resistance gene. Chloroplast transformation experiments were also performed with corn, rice, sweet potato and grape, but there is no disclosure of developed and fertile plants. Examples 3 and 4, disclosing transformation of corn and rice, state that mature plants were obtained, but there is no disclosure that the plants were fertile. The '391 patent provides no other guidance for regeneration of plants from transformed plant material.

The '391 patent discusses chloroplast transformation and states at col. 2, line 59 – col. 3, that stable integration of a foreign gene into the chloroplast genome of a higher plant has been reported only in tobacco. The '391 patent indicates that the only published report of foreign gene expression in a plant species other than tobacco is that of wheat leaves and embryos, but stable integration was not accomplished, and that stable integration of a foreign gene into the chloroplast genome of a monocotolydenous plant has never been reported. (col. 3, lines 1-6). At column 16, lines 6-12 state:

> Of greatest present interest are the major economically important crops like maize, rice, soybean, wheat and cotton. None of these plants to the inventor's knowledge, other than tobacco, has ever been stably transformed via the chloroplast genome, and none, including tobacco, have been stably transformed by a universal vector, as described herein.

The Examiner apparently assumes that, once transformation of the plastids is accomplished, regeneration of fertile transplastomic plants follows as a routine matter. However, regeneration of fertile transplastomic leguminous plants, was not a routine matter when the '391 patent was filed in 1998, and methods of producing such plants would not be possible until the invention of the present application. Even if a skilled person followed the teachings of the '391 patent and produced transformed chloroplasts using the universal vector, he would not be able to produce fertile transplastomic leguminous plants. Dufourmantel et al., Zhang et al., Bock et al. and Daniell et al. (2005), all of record in the present application, attributed the difficulties in producing transplastomic plants to technical difficulties, summarized in relation to leguminous plants by Zhang et al.:

> It is apparent that many obstacles need to be overcome such as a limited choice of regenerable target tissues and selectable markers, a low

> frequency of transformation, the poor regeneration of embryogenic tissue, and possible improvement of vector design and deliver, before plastid transformation technology can be readily applied to soybeans. (Page 42, left column, second full paragraph)

Indeed, the Abstract of Zhang et al., relied upon by the Examiner to support the present rejection, actually alludes to the problems encountered by persons skilled in the art:

> This result [i.e., transformation of soybean plastids, but failure to regenerate whole plants] does indicate that it should be possible to insert genes into the plastid genome of the important crop soybean if the overall methods are improved. (page 39, Abstract, last sentence)

The state of the art is corroborated by Bock, which was published in 2001, and provides a review of plastome transformation technology in basic research and plant biotechnology. Bock states at page 434, left column,

> However, the wide use of transplastomic technologies in plant biotechnology currently encounters one serious drawback: at present, chloroplast transformation is routinely available only for a single higher plant species, tobacco. This is because tobacco is by far the most easy-to-handle species in plant tissue culture, allowing for the development of highly efficient selection and regeneration protocols for the production of transgenic plants. Limitations in the currently available tissue culture systems are considered to be the main obstacle to the extension of transplastomic technologies to other species and, most importantly, to major crop plants. Although recently some progress was made with *Arabidopsis* and potato chloroplast transformation [98,99] as well as with the generation of (heteroplasmic) transplastomic lines in rice,[100] a complete protocol for the production of fertile transplastomic plants has not yet been reported for any other species but tobacco.

At the filing date of the '391 patent, methods for producing fertile transplastomic plants, except for tobacco were not known. The failure of persons skilled in the art to generate such plants was not through a lack of skill or desire for the plants. As discussed in Bock and Zhang et al., the failure of persons skilled in the art to produce fertile transplastomic plants was due to technical limitations in plastid transformation technology and regeneration protocols for the production of transgenic plants.

The Examiner found unpersuasive Applicants' arguments in the previously filed response that Dr. Henry Daniell implicitly acknowledged the '391 patent was not a disclosure of fertile

transgenic soybeans because of his statements in Daniell et al. (2005), in which he attributes the first successful fertile transplastomic soybean plants to Dufourmantel et al. [referring to Dufourmantel et al. 2003]. The Examiner found Applicants arguments unpersuasive because Daniell did not say that he attempted soybean transformation and was unsuccessful.

The Daniell et al. (2005) publication does not explicitly state that Dr. Daniell himself attempted soybean transformation and was unsuccessful. Daniell et al. does state, however, that

> [c]hloroplast genetic engineering of soybean was first attempted by Zhang *et al.* [49], with the objective of increasing its photosynthetic potential. The first successful development of the chloroplast genetic engineering technology by somatic embryogenesis and the generation of fertile chloroplast transgenic plants of soybean was reported by Dufourmantel *et al.* [23] ... All chloroplast transgenic plants were fully fertile and produced viable seeds.

The statements of Dr. Daniell himself, when viewed in conjunction with the disclosures of the '391 patent and the other art of record, clearly imply that his own previous attempts to produce fertile transplastomic soybean plants were unsuccessful, and that the '391 patent does not disclose fertile transplastomic leguminous plants. The contribution of Dr. Daniell as first author of the Daniell et al. (2005) publication, along with Dr. Dufourmantel, an inventor of the present application, as co-author, is a very clear implicit statement that previous attempts, including his own, were unsuccessful.

Applicants are not restricted to explicit statements by Dr. Daniell, the inventor of the '391 patent, to show that claims of a patent are not enabled. The situation in the present application is similar to *Plant Genetics Systems N.V v. DeKalb Corp.* 315 F. 3d 1335 (Fed. Cir. 2003), in which claims were held to be invalid as not enabled because the technology required to produce the claimed transformed cells was not in existence at the filing date of the patents. *Plant Genetics Systems* involved the claims of U.S. Patent 5,561,236 (the '236 patent), which were directed to plant cells having a heterologous DNA encoding a protein having acetyl transferase stably incorporated into its genome. The court concluded that stable transformation of monocot cells required undue experimentation on the filing date of the patent in 1987 and the claims were not enabled. The Court's conclusion was based on testimony and publications showing the state of the art at the filing date. The Court mentioned in particular a publication, published in 1990,

three years after the filing date of the '236 patent, which reported the first success in stably transforming monocot cells. The Court stated that "[r]eports of a first success after 1987 indicates failure or difficulty in or before 1987."

The Examiner alleged that Dufourmantel et al. demonstrates the '391 patent is enabled. Applicants respectfully submit that Dufourmantel et al. does not demonstrate that the '391 patent is enabled. Quite the contrary. As the discussion above shows, at the filing date of the '391 patent fertile transplastomic plants, other than tobacco could not be produced. The method of Dufourmantel et al. employs plant materials, vectors, and culturing conditions not disclosed in the '391 patent or known in the art at that time. The disclosure in Dufourmantel et al. of fertile transplastomic soybean plants is not merely the result of following the teachings of the '391 patent to get a predictable result. The patentees cannot rely on later-developed technology to supplement an insufficient disclosure in a prior dated application to make it enabling. (*Gould v. Quigg*, 822 F.2d 1074, 1077 3 USPQ2d 1302, 1304 (Fed. Cir. 1987), and *Plant Genetics Systems*) The specification, when filed, must enable persons skilled in the particular art to use the invention without undue experimentation.

The '391 patent does not anticipate the vectors of claims 7-8 and 13. The claimed vectors are suitable for leguminous plant plastid transformation. The sequences homologous with a zone of the plastome of the leguminous plant to be transformed, bordering the expression cassette, are therefore of sufficient length to allow integration of the expression cassette into the chloroplast genome. The homologous sequences therefore should not be interpreted to contain as few as two nucleotides, as asserted by the Examiner. The universal chloroplast vector disclosed in the '391 patent contains tobacco chloroplast flanking sequences, whereas the vectors of claims 7-8 and 13 contain sequences homologous with a zone of the plastome of the leguminous plant to be transformed.

The '391 patent also does not anticipate the methods of claim 14 and 15, as the methods in the '391 patent did not result in fertile transplastomic leguminous plants, and the methods were not performed with embryogenic tissues obtained from immature embryos of leguminous plants as required by claims 14-15.

In summary, the '391 patent does not anticipate claims 1-3, 6-8 and 13-15. For at least the reasons discussed above, the '391 patent does not provide an enabling disclosure of fertile

transplastomic plants, and thus does not anticipate the claims of the present application. Withdrawal of this section 102(e) rejection is again respectfully requested.

REJECTION UNDER 35 USC 103

At pages 4-7 of the Office Action, the Examiner maintained the rejection of claims 1-16 under 35 USC 103 as obvious over Maliga et al. (U.S. Patent 5,877,402; the '402 patent) in view of von Allmen (GenBank Accession No. X7675) for the reasons set forth in the Office Action mailed February 19, 2008.

Applicants again traverse this rejection. Applicants' remarks relating to this rejection in the response filed July 21, 2008 are incorporated herein by reference.

Claims 1-16 are directed to fertile transplastomic leguminous plants, transformation vector suitable for leguminous plant plastid transformation, and methods for obtaining fertile transplastomic leguminous plants.

In the present Office Action, the Examiner relied upon the Abstract of Zhang et al. to support the position that persons skilled in the art would be motivated to combined the teachings of Maliga et al. and von Allmen to produce the claimed fertile transplastomic plants, and that there was a reasonable expectation of producing the plants. The Examiner stated that the '391 patent claimed stably transformed transplastomic leguminous plants. She further asserted that, even presuming that other had failed, the history of science is full of examples of researchers succeeding where others failed; why would anyone think that soybean plastid transformation could never be done. Finally, the Examiner alleged that Applicants failed to explain why a person skilled in the art would think that Maliga in view of von Allmen would not work.

Maliga et al., U.S. Patent 5,877,402, discloses DNA constructs for transformation of plastids of multicellular plants and expression of foreign proteins in plastids. The DNA constructs comprise a transforming DNA which is targeted to a pre-determined location on the plastid genome and inserted into the plastid genome by homologous recombination with targeting segments comprising DNA sequences homologous to the predetermined region of the plastid genome. The transforming DNA contains a non-lethal selectable marker gene which confers a selectable phenotype on cells having plastids in which substantially all of the genomes therein contain the transforming DNA and at least one insertion site for an additional DNA

segment such as a DNA encoding a heterologous protein. Maliga et al. discloses plastid transformation in tobacco using DNA constructs in which the targeting sequences were tobacco plastid genome sequences.

von Allmen, GenBank Accession No. X7675, discloses soybean plastid DNA for rps12, rps7, 16s rRNA, tRNA-Val, NADH dehydrogenase and ORF 143.

Applicants respectfully submit that the Abstract of Zhang et al. does not provide motivation to combine the disclosures of Maliga et al. and von Allmen to produce the claimed invention. The Abstract of Zhang et al. states

> This result [i.e., transformation of soybean plastids, but failure to regenerate whole plants] does indicate that it should be possible to insert genes in to the plastid genome of the important crop soybean if the overall methods are improved. (page 39, Abstract, last sentence)

The Abstract of Zhang et al. gives no clear indication of which methods need improvement, nor does Zhang et al. provide any guidance for making the improvements. Zhang et al. recognized that a number of obstacles, such as choice of limited choice of regenerable target tissues and selectable markers, low frequency of transformation, the poor regeneration of embryogenic tissue, and possibly improvement of vector design and deliver, had to be overcome before plastid transformation technology could be readily applied to soybeans. (page 43, left column) Far from supporting the Examiner's position, Zhang et al. actually supports Applicants' arguments that there was no reasonable expectation of success in producing fertile transplastomic leguminous plants.

Whether the obviousness analysis is characterized as motivation to combine the references, or obvious to try, as the Examiner essentially alleges in the present Office Action, the result is the same. There was still no reasonable expectation of success of producing the claimed fertile transplastomic leguminous plants, and claims 1-16 are not obvious in view of the cited references.

As discussed above, it was well-recognized in the art that application of transplastomic technology to plants other than tobacco was hindered by limitations in transformation protocols and tissue culture systems. Indeed, Maliga et al. states at col. 28, line 62 – col. 29, line 8

> Because of the variety of ways in which foreign DNA can be introduced into plastids, the major limiting factor to applying the constructs and method of the invention to different species will be the amenability of those species to tissue culture and somatic regeneration of intact plants. This technology is being expanded at an ever-increasing pace, as demonstrated by the rapid advancements made over the last decade in culture and regeneration of important crop plants of the grass family (e.g., maize, sorghum, rice, wheat), species which had been recalcitrant to tissue culture for many years. Accordingly, as this technology expands to encompass new plant species, the plastid transformation method and constructs of the invention can be used on those new species.

Maliga and his co-inventors recognized that, at the time of filing of their patent, it was not possible for persons skilled in the art to produce fertile transplastomic plants, except possibly for a small number of species, using the teachings therein because the technology to culture and regenerate most species of plants was simply unknown. For leguminous plants, methods for regenerating fertile transplastomic plants were not known at the filing date of the present application, as shown by the Daniell et al. '391 patent, Bock, Zhang et al., Dufourmantel et al., and Daniell et al. (2005), all of record, and the discussion above. Even if, assuming for the sake of argument, a person skilled in the art were to be motivated by Zhang et al. to combine the teachings of Maliga et al. and von Allmen, he would not have been able to regenerate fertile transplastomic plants, because methods for regenerating fertile transplastomic plants were unknown, due to a number of art-recognized obstacles, discussed above, which prevented the production of the plants. Persons skilled in the art therefore had no reasonable expectation of producing fertile transplastomic leguminous plants, even if, for the sake of argument, they were motivated to attempt to produce them.

The Examiner commented that, even presuming others had failed, the history of science is full of examples of researchers succeeding where other failed; why would anyone think that soybean plastid transformation could never be done. Applicants do not have to show why anyone would think that soybean plastid transformation could never be done. Applicants only have to show that there was no reasonable expectation of success of obtaining the claimed fertile transplastomic leguminous plants in view of the combined the teachings of Maliga et al. and von Allmen. The absence of methods that could be used to produce fertile transplastomic plants was recognized in the art to be a problem, not only for leguminous plants, but also for every other

species of plant except for tobacco. There is no way of knowing whether persons skilled in the art believed that soybean transformation could never be done, but the state of the art when the present application was filed clearly shows there was no reasonable expectation of producing fertile transplastomic leguminous plants.

The claimed fertile transplastomic plants represent a major technical achievement. The methods of claims 14 and 15 overcome the technical problems known in the art which prevented persons skilled in the art from obtaining the goal of fertile transplastomic leguminous plants. In the methods of claims 14 and, the transformation step is performed using embryogenic tissues obtained from immature embryos of leguminous plants. Unlike prior art methods, the methods of the invention result in high frequency transformation of soybean plastomes leading to fertile transplastomic plants.

Applicants were the first to obtain fertile transplastomic leguminous plants. Prior to the present application, there were no reports of fertile transplastomic leguminous plants, despite attempts by Zhang et al. and attempts by Daniell in the '391 patent, which Dr. Daniell implicitly admitted were non-enabling in his later publication Daniell et al. (2005), discussed above. In view of the failure of others skilled in the art to produce fertile transplastomic plants, and the art-recognized obstacles to producing fertile transplastomic plants, except for tobacco, there was no reasonable expectation that fertile transplastomic leguminous plants could be obtained.

Claims 1-16 are not obvious in view of the '402 patent and von Allmen. Withdrawal of this section 103 rejection is again respectfully requested.

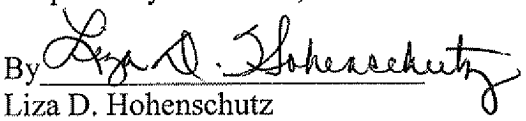
In view of the above, the present application is believed to be in a condition ready for allowance. Reconsideration of the application is respectfully requested and an early Notice of Allowance is earnestly solicited.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this

application by this firm) to our Deposit Account No. 03-2775, under Order No. 05500-00148-US. A duplicate copy of this paper is enclosed.

Dated: February 9, 2009

Respectfully submitted,

By 

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